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Review

The choice of systemic adjuvant therapy in receptor-positive early breast cancer

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Abstract

Patients with endocrine-responsive breast cancer represent a distinct population for which tailored adjuvant treatments are needed. Endocrine therapy is mandatory for this population. For premenopausal patients, ovarian ablation or tamoxifen can be recommended; the combination of both, as well as the combination of ovarian ablation and aromatase inhibitors is under investigation. For postmenopausal patients, tamoxifen for 5 years is the 'standard of care'. Anastrozole can be recommended for patients with a contraindication to tamoxifen. The addition of 5 years of letrozole after 5 years of tamoxifen has yielded benefits in terms of disease-free survival. The sequential use of tamoxifen and exemestane was superior to tamoxifen for 5 years. However, in both studies, long-term toxicity is still not fully evaluated. The addition of chemotherapy to endocrine treatment can be recommended for patients at high risk of relapse and in young patients. Chemotherapy should consist of 3–6 cycles of cyclophosphamide, methotrexate, 5-fluorouracil or of an anthracycline-containing regimen. The addition of taxanes cannot be routinely recommended in this population. Endocrine treatment should start after completion of chemotherapy.

Keywords: Breast cancer; Endocrine-responsive; Endocrine therapy; Chemotherapy; Ovarian ablation; Tamoxifen; Aromatase inhibitors

1. Introduction

Breast cancer is the most frequently diagnosed cancer in the Western world, with a lifetime risk in the more developed countries of one in eight women [1]. The incidence of the disease is continuously increasing, both in industrialised and developing countries, and more than 1 000 000 cases are diagnosed each year worldwide [2]. During recent years, mortality due to breast cancer has started to decline and the reasons for this have been widely debated [3].

Several features have been used for determination of prognosis, but the most reliable factor remains the nodal status [4]. Hormone receptors [5–11] (oestrogen receptors – ER – and progesterone receptors – PgR) and HER-2/*neu* overexpression [12] are the most important predictors of response to therapy. The proportion of ER-positive tumours is higher with increasing age and reaches approximately 90% in elderly patients [13]. The percentage of ER- and PgR-expressing cells discriminating between endocrine-responsive and endocrine-non-responsive tumours is unknown. Even a low number of cells (1%) staining positive may identify a cohort of tumours with some responsiveness to endocrine therapies [14]. Conventionally, approximately 10% of cells staining positive for both ER and PgR are considered as a reasonable threshold for the definition of endocrine responsiveness [4]. Gene expression profiling studies support a distinct pattern for steroid hormone receptor-absent disease compared with disease showing some or high levels of receptors [15–18].

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Systemic adjuvant therapy has been shown to reduce relapses in treated women and to prolong their survival. Treatments consist of cytotoxic agents, hormonal manipulations or a combination of both modalities [19]. Ongoing clinical trials are currently investigating the role of additional agents (trastuzumab, bisphosphonates, Cox-2 inhibitors, etc.) [20–24].

Evidence from clinical trials has been used to draw guidelines for the choice of systemic adjuvant therapy after surgery for breast cancer (for example, the International Consensus Panel during the St. Gallen Conference, 2003). Four issues must be considered for treatment decisions outside of the framework of clinical trials: prognosis, prediction of treatment response, extrapolation of results on treatment effects obtained from randomised trials, and consideration of patient's preference concerning absolute and relative risks and benefits of effective therapies [4].

2. Endocrine therapies

Long before the discovery of hormone receptors by Jensen in 1968 [25], endocrine therapies have been used for the treatment of breast cancer.

2.1. Ovarian function suppression

Ovarian ablation was the first form of systemic treatment for breast cancer. Its efficacy in metastatic disease was described by Beatson in 1896 [26]. The first randomised trials investigating ovarian ablation in the adjuvant setting began in 1948. The combined analysis of these early trials conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [27] has unequivocally established that ovarian ablation as a single intervention, whether induced by surgery or radiotherapy, is associated with a significant improvement in recurrence-free and overall survival among women less than 50 years of age. Indirect comparisons show that the magnitude of the benefit derived from ovarian function suppression is similar to that observed with adjuvant chemotherapy [28] or tamoxifen [29]. During the last 20 years, luteinising-hormone-releasing-hormone (LHRH) analogues have frequently substituted surgical or radiotherapy-induced ablation because of their ease of administration and the reversibility of their effects. Cytotoxic chemotherapy represents a fourth form of ovarian function suppression because of its capacity to cause temporary or permanent ovarian dysfunction in premenopausal women. The risk of chemotherapy-related amenorrhoea is directly related to age at the time of treatment and varies with type, dose, and duration of chemotherapy. In general, less than 50% of women below 40 years of age will be rendered postmenopausal by standard adjuvant chemotherapy regimens, whereas most women aged 40 or more years of age will become permanently menopausal [30–32]. Therefore, the possibility of fertility loss after adjuvant treatment for breast cancer should always be discussed with young patients with favourable prognosis prior to planning adjuvant strategies.

HER2/*neu* overexpression has been associated with a reduced responsiveness to endocrine therapy, particularly to tamoxifen. In premenopausal patients with tumours expressing HER2/*neu* the addition of ovarian ablation to tamoxifen has been shown to reverse non-responsiveness [33].

The combination of ovarian function suppression and tamoxifen in premenopausal patients has been investigated in a meta-analysis of four trials including 506 women with advanced breast cancer randomised to either LHRH agonist alone or to the combination of LHRH agonist plus tamoxifen. A significant survival ($P = 0.02$) and progression-free survival (PFS) benefit ($P = 0.0003$) were observed in favour of the combined treatment [34].

In the adjuvant setting, over 700 premenopausal women with early-stage breast cancer recruited in China and Vietnam have been included in a trial comparing oophorectomy and 5 years of tamoxifen, either at the time of mastectomy or at relapse. Preliminary results suggest that immediate combined treatment significantly improves the 5-year disease-free survival (DFS) and overall survival (OS) in patients with receptor-positive tumours compared with no immediate adjuvant therapy [35].

No study has yet been performed in the adjuvant setting to compare tamoxifen plus ovarian function suppression with tamoxifen alone in premenopausal women with endocrine-responsive disease. An ongoing global trial conducted by the Breast International Group (BIG) and the North American Intergroup (Trial SOFT) investigates the role of the combination of oophorectomy with tamoxifen or with the aromatase inhibitor exemestane compared with tamoxifen alone in the adjuvant setting [36,37].

2.2. Tamoxifen

Tamoxifen for 5 years has been shown in women with ER-positive tumours to reduce recurrence and contralateral breast cancer by approximately 50% and mortality by 28%. These benefits appeared to be independent of age, menopausal status and additional use of chemotherapy. Benefits from treatment are larger for patients treated for 5 years than for those receiving tamoxifen for a shorter period. No benefit could be observed for continuing tamoxifen treatment longer than 5 years [29].

Tamoxifen is associated with several side-effects including increased risk for endometrial cancer and thromboembolic disorders [38]. Investigations of bone